Transfusion Management of an IgA Deficient Patient With Anti-IgA and Incidental Correction of IgA Deficiency After Allogeneic Bone Marrow Transplantation

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A patient with multiple myeloma was noted to have an IgA deficiency during investigation of a possible transfusion reaction due to IgA deficiency and anti-IgA. Because of the patient's age, otherwise good health, and early stage of disease, he was enrolled in a research treatment protocol that involved an allogeneic bone marrow transplant (BMT). The BMT successfully put the patient in complete remission from his multiple myeloma and corrected his IgA deficiency. Class-specific IgG anti-IgA antibody that had been identified prior to BMT was no longer detectable in his plasma. Anaphylactic transfusion reactions were successfully avoided by using a combination of IgA-deficient and washed blood components including the marrow graft, and IgA-reduced intravenous immunoglobulin. Am. J. Hematol. 57:326–330, 1998.

Key words: IgA deficiency; anti-IgA; anaphylactic reaction; bone marrow transplantation

INTRODUCTION

Selective immunoglobulin A (IgA) deficiency, defined as serum IgA levels less than 0.05 mg/dL, is the most common primary immunodeficiency disorder, affecting between 1 in 200 and 1 in 1,000 individuals [1–3]. Serum IgG antibodies to IgA (anti-IgA) may be present in up to 44% of such patients [2]. Although anti-IgA occurs most commonly after exposure to IgA through transfusion or pregnancy, it can occur without any prior exposure to blood components. Anti-IgA antibodies are usually class-specific, reacting with all human IgA proteins, both IgA1 and IgA2 subclasses. Less commonly, anti-IgA antibodies have ''limited specificity,'' meaning the antibody reacts with IgA1 or IgA2 (subclass specificity) or IgA2m(1) or IgA2m(2) (allotypic-specificity) proteins [3–5].

Patients who are IgA-deficient and have anti-IgA in their serum are at risk for the development of severe allergic or anaphylactic reactions during transfusion of blood components and infusion of immunoglobulin. Most IgA anaphylactic transfusion reactions occur in IgA-deficient patients who have a class-specific anti-IgA antibody [4,6]. Such patients require IgA-deficient blood components for transfusion. This can be problematic for the hospital transfusion service when multiple units of blood components are required, as generally occurs during allogeneic bone marrow transplantation.

We describe the transfusion management of an IgA-deficient BMT candidate. We also report the first case of incidental correction of IgA deficiency and loss of anti-IgA following allogeneic bone marrow transplantation.

CASE REPORT

A 44-year-old Caucasian male presented to his local physician for a community-acquired pneumonia, which was successfully treated with oral antibiotics. The patient had an unremarkable past medical history, and he denied

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ever receiving a blood transfusion. Routine laboratory tests included a white blood cell count of 8,500 per μL (8.5×10^9/L) with a normal differential cell count, hematocrit (Hct) of 30% (0.30), platelet count of 460,000 per μL (460×10^9/L), and a creatinine concentration of 1.6 mg per dL (0.016 g/L). Serum protein electrophoresis revealed a 4.15-g/dL monoclonal spike, which was characterized as IgG kappa on immunofixation electrophoretic analysis. Radiographic skeletal survey was unremarkable. A bone marrow biopsy revealed a hypercellular marrow, which was focally replaced by aggregates of plasma cells. The patient was diagnosed as having multiple myeloma, stage 1, and was enrolled in a research treatment protocol.

The patient received four cycles of chemotherapy using vincristine, doxorubicin, and dexamethasone (VAD) followed by high-dose cyclophosphamide. During this treatment, the patient required a leukocyte-reduced, irradiated red blood cell (RBC) transfusion at an outside institution for symptomatic anemia due to chemotherapy. After transfusion of 15–20 mL of RBCs stored in additive solution AS-1, the patient developed an anaphylactic transfusion reaction characterized by tachycardia, hypotension, dyspnea, and wheezing. The transfusion was stopped and treatment with intravenous fluids, diphenhydramine, and hydrocortisone quickly reversed the patient's symptoms. The possibility of an anaphylactic transfusion reaction due to anti-IgA was considered.

Initial screening for IgA using rate nephelometry was performed on a specimen obtained 1 month after the anaphylactic transfusion reaction. Confirmatory testing performed by passive hemagglutination inhibition (PHAI) found undetectable levels of IgA. Anti-IgA was detected using two different methods: passive hemagglutination and enzyme immunoassay (EIA).

To support the BMT patient, only IgA-deficient plasma-containing blood components were provided for transfusion. All units of RBCs were washed prior to transfusion. None were from IgA-deficient donors. When apheresis platelet concentrates (PC) from IgA-deficient donors were unavailable, PC were washed prior to transfusion. The mononuclear cell collection (MNC) from the bone marrow harvest was concentrated and washed to avoid exposure to BMT donor plasma.

After a preparative regimen of Melphalan and total body irradiation, the patient received a BMT from his HLA genotypically identical sister who had normal serum IgA levels. During the post-BMT period, the patient received IgA-deficient, leukocyte-reduced, irradiated blood components including 7 U of packed red blood cells, and 12 apheresis platelet concentrates. Premedication with acetaminophen 650 mg po, diphenhydramine 50 mg IV, and hydrocortisone 100 mg IV occurred prior to each transfusion. Despite the number of transfusions, the patient did not experience any further transfusion reactions.

Beginning on day 30 post-BMT, he received 45 g intravenous immunoglobulin (IVIG), which was known to be relatively IgA-deficient (Gammagard, Baxter Healthcare Corp., Glendale, CA), every 2 weeks for 2 months. He tolerated IVIG infusions without any adverse reactions.

Six months after BMT and 3 months after the most recent exposure to IgA, the patient was in complete remission for his multiple myeloma. Repeat analysis of IgA levels and anti-IgA revealed the presence of low levels of IgA and no detectable anti-IgA antibody.

MATERIALS AND METHODS

IgA and Anti-IgA Testing

The patient's serum was initially screened for IgA using rate nephelometry (Array Protein Systems, Beckman Instruments, Inc., Brea, CA) according to the manufacturer's instructions. Confirmatory testing for IgA was initially performed by the National Reference Laboratory for Blood Group Serology, American Red Cross Blood Services, Rockville, MD, using hemagglutination inhibition and radial immunodiffusion. Testing for anti-IgA was performed using passive hemagglutination assays utilizing the method first described by Vyas et al. and modified by Fudenberg and Koiskinen [3,4,7,8]. Confirmatory testing for anti-IgA utilizing two different solid-phase enzyme immunoassays (EIA) was performed at the Finnish Red Cross Blood Transfusion Service, Helsinki, Finland, and our institution, respectively. One of the EIAs was developed by Koiskinen et al. and uses EIA plates directly coated with IgA [9]. The second EIA developed by Virella et al. in our institution (unpublished data) used EIA plates pre-coated with jacalin, to increase IgA adsorption (jacalin-primed EIA).

Bone Marrow and Blood Components

The patient was transplanted with ABO compatible bone marrow from his HLA-matched sister. The mononuclear cell concentrate (MNC), obtained by layering the bone marrow onto a light density gradient, was then washed (3 wash cycles) with 2 L of Plasma-Lyte A (Baxter Healthcare Corp., Deerfield, IL) and resuspended to a volume of 60 mL yielding a dose of 1.58×10^8 MNC/kg recipient body weight.

Red blood cells were washed (3 wash cycles) prior to transfusion using a Cobe 2991 Blood Cell Processor (COBE Laboratories, Lakewood, CO) and 2 L 0.9% sodium chloride as the wash solution. Either apheresis platelets from IgA-deficient donors or washed PC from non-IgA-deficient donors were provided for this patient. Platelet washing (3 wash cycles) was performed utilizing an automated platelet washing technique [10] and modi-

TABLE I. Results of Pre-BMT IgA Testing

Test method	Results	Adult normal values (mg/dl)	Level of sensitivity (mg/dl)[a]
Radial immunodiffusion	Precipitin ring detected	75–420	7
Rate nephelometry	<6.7 mg/dl	69–309	6.7
Hemagglutination inhibition	No IgA detected	IgA present	0.1

[a]As indicated by testing laboratory.

fied by using 2L Plasma-Lyte A (Baxter Healthcare Corp.) wash solution.

RESULTS

Results of pre-BMT testing for IgA and anti-IgA are shown in Tables I and II, respectively. Six months after BMT, the patient's serum was retested for IgA and anti-IgA by the ARC National Reference Laboratory for Blood Group Serology. The results are shown in Table III.

TABLE II. Results of Pre-BMT Anti-IgA Testing

Test method	Results	Adult normal values
Passive hemagglutination	Class-specific anti-IgA present titer: 160/80[a]	No anti-IgA present, titer: <80
Solid-phase EIA	Titer: 20	Titer: ⩽20
Solid-phase EIA[b]	55 AU/L	<35 AU/L

[a]160: American Red Cross; 80: Finnish Red Cross.
[b]Finnish Red Cross.

TABLE III. Results of Post-BMT IgA and Anti-IgA Testing

Test method	Results	Adult normal values
IgA		
Hemagglutination Inhibition	IgA present	IgA present
Radial Immunodiffusion	No precipitin ring detected	75–420 mg/dL
Anti-IgA		
Passive Hemagglutination	No Anti-IgA detected	No Anti-IgA detected

DISCUSSION

Three important points arose during the patient's care, which made management of this BMT extremely challenging. First, the need, pre-BMT, to identify the etiology of the anaphylactic transfusion reaction, which required a thorough understanding of the testing algorithm and sensitivities of the various assays for IgA and anti-IgA. Second, provision of IgA-deficient blood components and IVIG was necessary to reduce the risk of anaphylaxis throughout the patient's hospitalization. Third, incidental correction of IgA deficiency and loss of anti-IgA after successful BMT for multiple myeloma was observed.

An anaphylactic transfusion reaction is a medical emergency. After stopping the transfusion, laboratory investigation of the etiology of the transfusion reaction should begin. The possibility of an anaphylactic transfusion reaction due to anti-IgA should be considered and a screening test to determine the patient's serum IgA level should be performed. If possible, the screening test should be performed on a pretransfusion serum specimen because a post-transfusion specimen may falsely elevate IgA levels due to passive transfusion of donor IgA. Screening tests for IgA, such as radial immunodiffusion (RID) and nephelometry, are rapid tests, but they are relatively insensitive to low concentrations of IgA. Their major function is to identify the patient who has detectable IgA because that patient is unlikely to develop an anaphylactic transfusion reaction when transfused with standard blood components. In this group of patients, IgA-deficient blood components are not indicated [4].

If the screening test demonstrates IgA deficiency, then a more sensitive confirmatory test such as passive hemagglutination inhibition (PHAI), radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA), which can detect IgA concentrations less than or equal to 0.05 mg/dL, should be performed [1,3].

A standard assay such as passive hemagglutination should also be performed to detect anti-IgA. Used by the American and Canadian Red Cross Reference Laboratories, it is the most common method used for detecting anti-IgA [4].

The assays used to detect IgA and anti-IgA in the patient presented here showed consistent results of IgA deficiency with anti-IgA with two exceptions. Rate nephelometry, with a level of sensitivity of 6.7 mg/dL at our institution, showed IgA deficiency, which was confirmed by the more sensitive assay, PHAI. In contrast, RID, which has a level of sensitivity similar to rate nephelometry, indicated the presence of IgA based on the formation of a precipitin ring. In this instance, the precipitin ring was probably caused by cross-reactive antiruminant antibodies. In patients with IgA deficiency, IgG antibodies against ruminant serum proteins are common [11–13].

Class-specific anti-IgA was screened by PHA and two different solid-phase EIA, one using IgA-coated plates,

which has been shown to correlate well with PHA [9], and another in which the EIA plates are pre-coated with jacalin (unpublished data). Low titers of antibodies were detected by PHA and one of the EIA, but not by the jacalin-primed EIA. It should be noted that even in the positive assays, the levels of anti-IgA antibodies were low, not in the range usually associated with hypersensitivity reactions. The discrepancy between the two EIA is likely to reflect the known inaccuracy of this assay when the antibody levels are low [9].

When the patient has been shown to be IgA deficient, only IgA-deficient blood components should be transfused until the results of the anti-IgA assays are available. If anti-IgA antibodies are not identified, transfusions with standard blood components may be cautiously resumed. If anti-IgA antibodies are identified, the patient must receive only IgA-deficient blood components and IVIG.

IgA-deficient RBC, platelets, plasma, and cryoprecipitate can be obtained from IgA-deficient donors [3,4]. IgA-deficient RBC can also be obtained as frozen deglycerolized (washed) RBCs or by multiple washings of standard RBC using an automated cell washer [4]. IgA-deficient platelets can also be obtained by multiple washings of standard platelets [10,14–17]. IgA-deficient plasma or cryoprecipitate must be obtained from IgA-deficient donors. Although the IgA concentration in blood components that can be tolerated by patients with anti-IgA is unknown, it is recommended that IgA-deficient donors have serum IgA levels less than 0.05 mg/dL [18].

The frequency of IgA deficiency in random blood donors is similar to that found in the random population, so findings IgA-deficient donors can be difficult [5]. Regional blood collection centers may have a registry of IgA-deficient donors. The American Red Cross Rare Donor Registry and the American Association of Blood Banks Rare Donor File may provide additional sources for IgA-deficient donors.

Intravenous immunoglobulin has been used in allogeneic BMT in an attempt to decrease the incidence of infections and graft vs. host disease [19]. Although IVIG contains primarily IgG, varying concentrations of IgA are present. Thus, adminstration of IVIG is generally contraindicated in patients with IgA deficiency who have developed anti-IgA due to potentially fatal anaphylactic reactions. Only 2 of the IVIG products studied by Apfelzweig et al. had IgA concentrations of less than or equal to 1.0 mg/dL; the majority had IgA concentrations greater than 15.0 mg/dL [20]. The content of IgA in IVIG below which patients with anti-IgA will not have a severe allergic or anaphylactic reaction is not known. The patient presented here tolerated infusion of IgA-depleted IVIG, which, according to the manufacturer's circular of information, had less than 0.37 mg/dL (when reconstituted in a 5% solution) without any infusion reactions.

The ability of this patient to tolerate low levels of IgA was similar to the findings in a study that evaluated the use of IgA-depleted IVIG in patients with anti-IgA. Patients who had received IVIG with an IgA content ranging from 27.0–72.0 mg/dL had a history of severe infusion reactions. When they were switched to IgA-reduced IVIG (Gammagard) with an IgA content ranging from 0.04–0.29 mg/dL, they experienced only mild to moderate infusion reactions, which typically consisted of shaking chills, rigors, hives, or myalgias. None of the patients developed hypotension, shortness of breath, cyanosis, or chest pain after infusion of IgA-reduced IVIG [21].

We believe the patient described in this report is the first reported case of incidental correction of selective IgA deficiency and loss of anti-IgA in a patient who received an allogeneic BMT. There is a single previously reported case of incidental correction of selective IgA deficiency in a 3-year-old female who underwent allogeneic bone marrow transplantation for Gaucher's disease [22]. She reportedly did not have anti-IgA. In both cases, the bone marrow came from a donor with normal levels of IgA.

Our patient had detectable serum IgA and no detectable anti-IgA at 105 days and again at 6 months post-BMT. Because the patient had no detectable IgA production pre-BMT, the post-BMT findings are presumed to represent IgA synthesis by donor lymphocytes. It takes 3 to 6 months after engraftment before IgA-producing B cells are present in the circulation of post-BMT patients [23]. It is unlikely that the low level of IgA identified post-BMT in our patient represented passive transfer of IgA from either intravenous immunoglobulin or transfusion of plasma containing blood components because, due to the 6-day half-life of IgA, any passively transferred IgA would have been depleted during the 3 months between the patient's last exposure to IgA (IVIG) and the post-BMT IgA and anti-IgA quantitations [24].

In conclusion, in this patient with selective IgA deficiency and anti-IgA who underwent BMT, incidental loss of anti-IgA and correction of IgA deficiency occurred. The risk of anaphylaxis was reduced by providing IgA-deficient blood components, IgA-reduced IVIG, and washing the MNC collection to reduce exposure to donor plasma.

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